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OFFICE OF
THE ADMINISTRATOR
EPA SCIENCE ADVISORY BOARD

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The SAB is not soliciting comments on the advice contained herein. However, as a courtesy to the EPA Program Office, which is the subject of the SAB review, we have asked them to respond to the issues listed below. Consistent with SAB policy on this matter, the SAB is not obligated to address any responses that it receives.

1. Has the Committee adequately responded to the questions posed in the Charge?
2. Are any statements or responses made in the draft unclear?
3. Are there any technical errors?

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I. EXECUTIVE SUMMARY

On November 20-22, 2002, the Human Health Research Strategy Review Panel ("The Panel;") met to provide advice on four charge questions relating to the strategic directions for the USEPA Office of Research and Development's (ORD) core research program in human health risk assessment over the next five to ten years. The research directions were based on the evaluation of research needs from the Agency's regulatory and regional programs and consideration of recommendations from external advisory groups. The research strategy discusses the major environmental problems, the principal scientific issues, and the priority research areas that need to be addressed in order to resolve the problems. The priority research areas identified in the Human Health Research Strategy (HHRS) document include (1) research on harmonizing risk assessment approaches, (2) research on aggregate and cumulative risk (3) research on susceptible and highly exposed subpopulations and (4) research to enable evaluation of public health outcomes.

The panel has therefore provided comments and recommendations in the context of these four areas of research focus to address the following charge questions: (1) Does the document establish the appropriate direction and research areas (i.e., aggregate-cumulative risk, harmonization, susceptible subpopulation, effectiveness of public health outcome) for a long-term, core research program on human health risk assessment? (2) Will the research that is described reduce uncertainty in the risk assessment process? (3) For the research areas selected, does the strategy provide a clear framework for a multi disciplinary research program? (4) Does the strategy provide a logical approach for framing research to evaluate the impact of risk management decisions on human health?

The Agency has clearly invested a substantial amount of expertise, time, and energy into HHRS document. The panel agrees that the overall goals outlined in the human health strategy are commendable and represent a significant step towards overcoming the limitations of current risk assessment methods. The Agency has clearly invested a substantial amount of expertise, time, and energy into this document, entitled, "Human Health Research Strategy". However, the panel has identified specific issues that require further consideration. The panel's major comments and recommendations are as follows:

Research on the harmonizing risk assessment approaches

The *HHRS document* specifically includes "harmonization" of approaches to risk assessment for cancer and other adverse health outcomes (i.e., "non-cancer" effects). The panel interprets this focus as evidence of the Agency's over-arching commitment to applying the most complete scientific understanding in support of health protection. In that regard, the panel believes that true "harmonization" will be best achieved by fully considering information on mechanisms / modes of action in risk assessment. Strategic research planning should focus on advancing such knowledge, while recognizing that "[harmonization] does NOT mean that a single methodology should be used for assessment of all toxicities and pollutants."

The section on harmonization[a] is focused on developing principles and guidelines for "drawing inferences from scientific information" and stresses that methods [what kind of methods… modeling? not clear and what does consistently mean in this context?] should be consistently applied to toxicity, dosimetry, mode of action, and exposure data in constructing risk assessments. Consequently, the research undertaken will concern exposure, dose, effect, and risk assessment methodology. The panel applauds the idea of developing mechanism-based techniques and rather than be limited to an approach rigidly dichotomized between cancer and non-cancer endpoints when scientifically appropriate. In addition, Agency research should address the need to integrate information from animal studies with the results of studies in humans (experimental or epidemiological). Such an approach is likely to yield new insights through cross-fertilization of ideas within an interdisciplinary environment. Moreover, given the development of new powerful computer-based modeling and bioinformatic methodologies, [are these methodologies or tools?], this is an opportune time to develop such a strategy.

Research On Aggregate And Cumulative Risk

The panel agrees that focus on aggregate and cumulative exposure and risk is an appropriate and logical next step in the evolution of human health risk assessment. The HHRS document recognizes the importance of reducing uncertainties in all aspects of the source-to-effects continuum. Nonetheless, it would benefit from further elaboration on and a more balanced presentation of areas of research needs and, in particular, the allocation of resources necessary for elucidating the events leading up to exposure, since knowledge and understanding of these events is crucial for developing effective risk management and public health protection decisions. Our ability to characterize these events will be crucial in not only the assessment of aggregate and cumulative risk but also in identifying highly exposed subpopulations and relating risk management decisions to health outcomes. The HHRS should incorporate a more thorough description of current exposure-related research within the ORD, the future direction of these efforts, and their integration the other research areas described in the document. . Continued improvements in communication and interactions across disciplines within and between scientists in the NERL and NHEERL research programs, as well between ORD researchers, academia, and public health agencies should continue to be emphasized.

Research On Susceptible And Highly Exposed Populations

Susceptibility embodies the fundamental question in risk assessment, that is, "Who is[when] at risk?" It embodies the role of predisposing factors including genetic factors, gender, age, and disease [and immune] status in determining how an organism will respond to chemical or physical agents. It must also include contributory risks, such as the impact of lifestyle, neuropsychological factors including stress, and living conditions, such as socioeconomic factors, passive smoking, and nutrition. These factors will have significant impact on the effects of environmental chemicals on human health. These interactions require further study and need to be included in a comprehensive strategy.

[a] *Harmonization* in this context refers to the development of a consistent set of principles and guidelines for drawing inferences from scientific information. It does not mean that a single methodology should be used for assessment of all toxicities and pollutants. Page 2-2, lines 24 - 27.

In the HHRS document, there is an emphasis on the development and application of animal models in assessing the interaction of disease states and stage of development on susceptibility. Animal models may be best employed to understand mechanisms of toxicity. Extrapolations of risk estimates from animal data to risk assessments in humans, although frequently necessary, are difficult to conduct. There should be coordination between animal research and human research, but the reliability and applicability of some animal models as representative of the human condition must be carefully determined. Too much emphasis is currently placed on screening rather than on the deeper analyses that are suited for extrapolation to human risks. It is important to realize that for certain human diseases relevant animal models may not be currently available. The impact of stages of life, disease states, and genes on exposure and all aspects of pharmacokinetics/pharmacodynamics (PKPD should be addressed in full by the Agency. The program should direct more effort toward defining, understanding, and identifying specifically the most susceptible individuals in the human population in a host of disorders that can be altered or induced by the environment, such as neuropsychological dysfunction, asthma, cancer (polymorphisms in DNA repair enzymes), and endocrine and developmental dysfunctions.

Research To Enable Evaluation Of Public Health Outcomes From Risk Management Actions

In considering public health outcomes, the panel recommends the Agency provide a clear delineation of which public health outcomes are to be addressed. Furthermore, the conceptual details of the methodological approaches to be used in the evaluation of risk management actions are needed. In the HHRS document, epidemiologic research is used as a generic term without consideration of specific study designs and purposes such as cohort or case control approaches, molecular epidemiology, time series studies, and exposure assessment modules such as biomonitoring or population exposure models. The panel also recommends that concepts of population-based epidemiologic research such as attributable or preventable risk, competing risks, sentinel health events, body burden, and other related concepts be addressed explicitly. Because this chapter is incomplete, it is difficult to evaluate the intended research strategy. Although it is clear that partnering with other agencies and secondary data analysis will be pivotal in any strategy to be developed, this must be preceded by clarifying the public health outcomes of interest.

In closing, the panel would again like to reaffirm their support for the integrative, multidisciplinary approach that the Human Health Research Strategy appears to embrace. In implementing the strategy, additional attention should be focused on the suggestions put forth in this review document. Issues such as the rigorous evaluation of methods and models for their utility and applicability are essential to achieving the goal of improving risk assessment. Defining, understanding, and identifying the most susceptible populations, in addition to increased detail concerning the public health outcomes to be studied and the methods to be used will assist in focusing the effort and resources needed to meet the expectations outlined in the HHRS document. The panel also encourages the Agency to work in conjunction with state and federal agencies, as well as academia and research centers as it implements this strategy.

II. INTRODUCTION

The mission of the U.S. Environmental Protection Agency (EPA) is to protect public health and safeguard the natural environment (i.e., air, water, and land). Risk assessment is an integral part of this mission in that it identifies and characterizes environmentally related health problems. The EPA's Office of Research and Development (ORD) conducts research that contributes to the scientific foundation for risk assessment and risk management decisions in EPA's regulatory programs. Since 1996, ORD has used a risk-based strategic planning process in consultation with EPA's Program and Regional Offices and the external scientific community to set research priorities. From this process, research to improve human health risk assessment was identified as one of six priority research areas in the *1997 Update to ORD's Strategic Plan* (U.S. EPA, 1997a) and *ORD Strategic Plan* (U.S. EPA, 2001b). As such, fundamental human health research is also part of the ORD Sound Science Program under Goal 8, which is one of EPA's ten strategic environmental goals in accordance with the requirements of the Government Performance and Results Act (GPRA).

The *Human Health Research Strategy* (HHRS) document presents a conceptual framework for future human health research by EPA's Office of Research and Development (ORD). This research strategy outlines ORD's core research effort to provide broader, more fundamental information that will improve understanding of problem-driven health risk issues encountered by the EPA's Program and Regional Offices. The scope of this research document is strategic in that it discusses broad themes and general approaches. Implementation of an integrated research program on human health is described in greater detail in ORD's Multiyear Plan on Human Health Research.

The Multiyear Plan identifies specific performance goals and the measures needed to achieve those goals over a 5 to10 year period. Each Laboratory and Center in ORD is also developing an approach linking research at the project level to the goals and measures in the Multiyear Plan and the general themes outlined in the HHRS document. Based on the needs of the EPA's Program and Regional offices, recommendations made by external advisory groups, and goals established by EPA in response to the Government Performance and Result Act (GPRA) under Sound Science (Goal 8), ORD has identified two strategic research directions that will be pursued over the next 5 to 10 years.

The first, Research to Improve the Scientific Foundation of Human Health Risk Assessment, aims to reduce critical uncertainties in the state of the science of human health risk assessment through research targeted at three specific areas – harmonizing cancer and non-cancer assessments, assessing aggregate and cumulative risk and determining risk to susceptible human subpopulations. The second strategic direction, Research to Enable Evaluation of Public Health Outcomes from Environmental Risk Management Decisions, is more application-oriented in that it aims to use both existing and new human health risk assessment methods and techniques to evaluate the public health impact of regulatory decisions. Research in these two strategic areas is expected to improve the scientific foundation for EPA's risk assessments and lead to principles that can be used to evaluate the effectiveness of risk management actions aimed at improving environmental public health.

III. ASSESSMENT OF HARMONIZATION STRATEGY

The section on harmonization[b] within the HHRS document is focused on developing principles and guidelines for "drawing inferences from scientific information" and stresses that methods should be consistently applied to toxicity, dosimetry, mode of action, and exposure data in constructing risk assessments. Consequently, the research undertaken will concern exposure, dose, effect, and risk assessment methodology.

The HHRS document specifically includes "harmonization" of approaches to risk assessment for cancer and other adverse health outcomes (i.e., "non-cancer" effects). The panel interprets this focus as evidence of the Agency's over-arching commitment to applying the most complete scientific understanding in support of health protection. In that regard, the panel believes that true "harmonization" will be best achieved by fully considering information on mechanisms / modes of action in risk assessment. Strategic research planning should focus on advancing such knowledge, while recognizing that "[harmonization] does NOT [emphasis added] mean that a single methodology should be used for assessment of all toxicities and pollutants."

The panel applauds the idea to develop mechanism-based methodologies and to do away with different approaches in conducting risk assessments on cancer and non-cancer endpoints when scientifically appropriate. Such a new approach is certain to yield new insights as well as to generate an exciting research environment that will promote an interdisciplinary environment leading to the cross-fertilization of ideas. Moreover, given the development of new powerful computer-based modeling and bioinformatic methodologies, this is an opportune time to develop such a strategy.

The HHRS document emphasizes that the research will involve effects of environmentally relevant doses or concentrations of those pollutants selected for study. The panel advises that the strategy state that both high and low doses be studied in order to elucidate the likely shape of the dose-response curve and to determine whether different modes or mechanisms of action may be operating at low and high doses. Too often, there is unwarranted reliance on extrapolating from high dose effects and corresponding mechanisms into the low dose region where there is an entirely different mode or mechanism in operation.. For example, on p.2-2, there is a discussion of non-genetic processes for cancer and non-cancer effects, such as cell death leading to tissue regeneration and tumor formation. However, it needs to be recognized that this process is driven by the high doses common in laboratory animal studies and some occupational settings, not from ambient exposure situations. Attempts to incorporate mechanism / mode of action data into risk assessment need to consider repair as well as background rates of cell death/division which may, in some cases, dwarf those induced by low-level exposures. There

[b] *Harmonization* in this context refers to the development of a consistent set of principles and guidelines for drawing inferences from scientific information. It does not mean that a single methodology should be used for assessment of all toxicities and pollutants. Page 2-2, lines 24 - 27.

is an excellent opportunity herewith to assure that any risk assessment is using the appropriate endpoint effect and the mode/mechanism of action that is appropriate at specified exposures.

The statement (in the form of a promise) in lines 24-28 on page 2-5 of the HHRS document states that, "ORD's effects research will lead to BBDR models that take into account the sequence of early biological events leading to adversity (i.e., mechanisms or modes of action) for multiple endpoints, the shape of the dose-response curves at low doses, and the influence of interspecies differences." This may be overly optimistic, because achieving these goals will be dependent on developments in laboratory research and epidemiology.

The five research objectives outlined on page E-3 of the HHRS show a serious deficiency in the strategy. The promise of advancements in risk modeling is not accompanied by a critical commitment to developing the underlying biological data necessary for such advancements. The third objective is, arguably, the best example. A model to "...compar[e] risk across all health endpoints using mechanistic information..." is the promise; unfortunately, insufficient emphasis is given to developing the necessary mechanistic information. Mechanistic knowledge must provide the basis for developing such models.

A brief passage, beginning at the bottom of page 1-11 (continuing on page 1-12) deserves note. The statement says, "Research on harmonizing risk assessment addresses the need to develop a consistent approach for the use of mechanistic information in all health risk assessments." This sentence is a blur of two almost-totally-independent ideas. Whether harmonization is needed (i.e., a single approach, regardless of the toxicological end-point) is open to debate. But, in any case, it is a question that is totally separate from whether the use of mechanistic data is the best choice / basis for that harmonization. The panel suggests that the two questions should be addressed separately - and successively - in the strategic plan. For all practical purposes, "yes" answers to both questions have been taken as "articles of faith," entirely without challenge or study.

Although one aspect of the HHRS document is research efforts to reduce uncertainty, the proposed use of emerging technologies such as genomics, proteomics and *in silico* methods (including, computational toxicology and bioinformatics) could actually increase the uncertainty of risk assessments and lead to faulty risk management paradigms. What is badly needed is standardization and validation of these technologies run side by side using conventional toxicity, exposure, and dose and effect methodology. Genomics, proteomics and *in silico* methods cannot, in and of themselves, serve as diagnostic tools to discern toxicological pathways leading to adverse effects unless they have been rigorously validated. This will require a substantial investment in equipment as well as expertise in molecular biology, genomics, bioinformatics, computer modeling. While from a research perspective these are exciting possibilities, it might be wise to wait until current research [including the NIEHS' toxicogenomics] can be evaluated to determine whether this is a fruitful avenue to develop within EPA to fulfill this part of the Strategy. In the event that the subsequent decision is to proceed, decisions will have to be made regarding whether *in vitro* or *in vivo* specimens will be studied etc.

The HHRS document suggests [p. 2-6] that the current endocrine disrupters effort will provide a "proof-of-concept". While that endeavor is extensive and will be able to rely on appreciable data, still the question needs to be asked: is this a good model for all health effects? The health effects of endocrine disrupters can be expected to be receptor-mediated. Most health effects of concern can occur by mechanisms that do not necessarily involve receptors. In any case, absent extensive knowledge of the mechanism / mode of action, the study of endocrine disruption does not lend itself to "proof of concept."

The HHRS document is also proposing to generate a proof-of-concept using endocrine disrupting chemicals because ORD had experience in determining environmental exposure levels to these chemicals and in developing *in vivo* and *in vitro* tests. For these multiple agents which ones should be chosen for study, those that affect male fertility, female fertility, cancer, thyroid disorders, immune disorders, child development, precocious puberty, autism, or wildlife? Is this relevant to real world exposures? The panel suggests selecting 2 or 3 adverse endpoints of concern that will allow for a stepwise process to reduce uncertainty and for developing a paradigm for future risk assessments that perhaps could become more reliant on panomics (aka, genomics, proteomics, and transcriptomics) and *in silico* techniques (including, computational toxicology and bioinformatics). The panel advises that the Agency revisit the agents, circumstances of exposure and adverse health effects (as denoted in Appendix A of the HHRS document) to consider whether there are more promising case studies for "proof of concept" efforts than is afforded by the study of putative endocrine disruptors.

The HHRS document states on line 30, page 2-7, to line 2, page 2-8, that "An important focus of ORD's risk assessment research on harmonization will be the development of approaches to characterize variability and uncertainty in reference toxicity values and to provide a probabilistic framework for estimating risks associated with exposures above the reference toxicity values." That sentence is neither a statement of research goals...nor is it useful guidance. Indeed, it's a pre-emptive judgment that current risk assessment methods (probabilistic) should replace current safety assessment methods (deterministic) in all cases.

Again, an unnecessary and restricting condition is placed on the research plan in lines 7-10, page 2-8, namely, that a specific tool (categorical regression) will be the tactical focus for applying the research results. With that said, the same sentence correctly, and clearly, states the desirable strategic goal of developing risk / safety assessment tools that can, in turn, inform assessments of costs and economic benefits. A much stronger emphasis should be made on research to advance the goals of improving the basis for assessments of costs, substitution risks, and benefits. To the extent that economic components are raised in the HHRS document, there should be commensurate economic research strategies proposed the can be evaluated by scientific peer review.

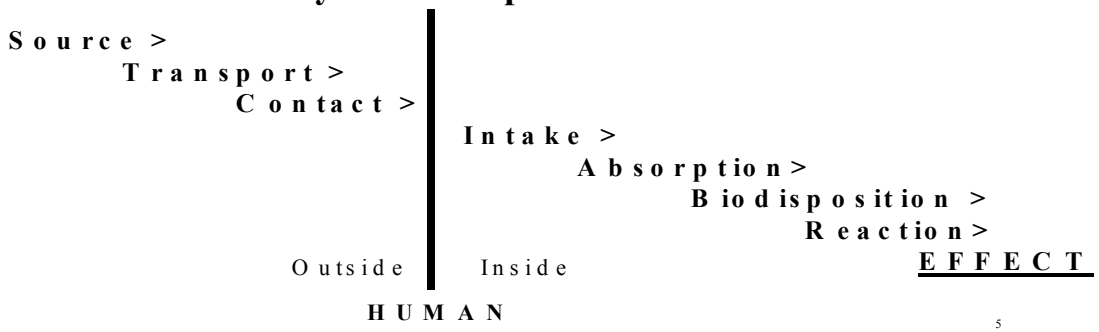
Although, much time and effort have gone into preparing the plan, before the promise of this plan can be realized, at least two improvements are necessary. First, the plan must be revised to provide truly strategic guidance, complemented by justification(s) for the strategic direction. Second, a clear and concise set of metrics must be agreed upon. Those metrics must be employed to assess the performance of the research program, to enhance that performance, or to redirect resources, if necessary.

In order to provide a clear framework for a multi disciplinary research program, the strategy should fully recognize the important contributions from the public health community, through population-based research. To the extent that ORD research on risk assessment methods will focus on how to incorporate mode-of-action information for health endpoints, the panel believes an appropriate framework has been outlined. The Agency does realize that as it moves forward with this research strategy, pressure will be brought in the form of an "onslaught of data generated" by the new panomics technologies and that these approaches "will far outpace the research and guidance on interpretation and application in risk assessment". Nevertheless, the EPA strategy is greatly preferred to the impulsive or inappropriate interpretation of poor quality data from badly designed studies. The EPA ORD approach is sound and logical.

IV. AGGREGATE AND CUMULATIVE RISK

This component of the Strategy presents a good foundation for improving the scientific merits of risk assessment, but one that would benefit from adding a significantly greater level of direction especially related to prioritization of the broad range of research efforts.. The scientific elements of human health risk assessment are nicely illustrated in Figure 1-3 of the HHRS document.

Figure 1.
Cause & Effect Continuum and the Boundary of Exposure Assessment



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The source-to-effect continuum in Figure 1-3 clearly shows the relationship between the output (modeled or measured) from each step along the way, and the input to the next step or process. By analogy, errors or uncertainties related to early events on the continuum could only propagate and grow throughout the entire process. As a result, these uncertainties will not only impact prospective analysis such as aggregate/cumulative risk and efforts to identify highly exposed subpopulation, but also retrospective analyses needed to relate biomarker data to exposure, or to evaluate the health outcomes related to risk management decisions. The document would benefit from a more thorough discussion of the uncertainties in the source to exposure linkages,

particularly in the Executive Summary, the Introduction and in the relevant sections under Scientific Uncertainties (i.e., Section 2.2.1 and 3.2).

While the panel agrees that exposure assessment represents fully half of the risk assessment paradigm, as a scientific discipline, exposure assessment is dramatically underdeveloped and very much behind the scientific progress of toxicology. Indeed, the scientific and technological foundations of toxicology are well established. Unfortunately, the same cannot be said of exposure assessment where our knowledge and understanding of the most fundamental determinants of exposure are missing. For example, there is a dearth of knowledge on 1) indoor source strengths and building material emission profiles, 2) indoor absorptive sinks and chemistry; 3) outdoor to indoor penetration factors; 4) near-field exposure; 5) dermal transfer factors; 6) the effect of HVAC systems on indoor source emission rates, transport, fate and concentrations, 7) activity patterns, and 8) model evaluation. Thus, these gaps and opportunities should represent a vital piece of research planning.

Since the outputs from sources become the inputs to transport, errors or lack of knowledge within the realm of sources or other early events on the continuum can only propagate and grow throughout the entire risk assessment process. Further, knowledge and understanding of the elements and processes that reside on the "Outside" part of the diagram are crucial for the design and formulation of risk management decisions that effectively reduce the effects on the "Inside" part of the continuum. Although the HHRS document does establish the appropriate direction and research areas for a long-term, core research program on human health risk assessment; as written, it does not reflect a balance in the need for research on uncertainties in the pre-exposure links of the risk paradigm as compared to the post-exposure components. While the panel agrees that exposure assessment represents fully half of the risk assessment paradigm, it is also safe to say that, as a scientific discipline, exposure assessment is dramatically underdeveloped and very much behind the scientific progress of toxicology. Indeed, the scientific and technological foundations of toxicology are well established and cutting-edge technical advances and programs in the realm of physiologically based pharmacokinetics and toxicogenetics are well along. The same cannot be said of exposure assessment where our knowledge and understanding of the most fundamental determinants of exposure are missing. For example, there is a dearth of knowledge on 1) indoor source strengths and building material emission profiles, 2) indoor absorptive sinks and chemistry; 3) outdoor to indoor penetration factors; 4) near-field exposure; 5) dermal transfer factors; 6) the effect of HVAC systems on indoor source emission rates, transport, fate and concentrations, 7) activity patterns, and 8) model evaluation. Thus, these gaps and opportunities should represent a vital piece of research planning.

Specific research objectives described in the HHRS document indicate a general movement towards more mechanistically based cellular-level research and *in-silico* modeling approaches to better characterize the dose-response relationship. Chemical source, environmental fate, transport and exposure models that are needed to support aggregate/cumulative analyses are often based on empirical and/or theoretical relationships that, in the opinion of this panel, have not been fully developed or adequately evaluated for accuracy.

These pre-exposure elements of the source-to-risk continuum are identified in the current plan but they are not prominently recognized and outlined as critical early tasks for intensive or ongoing research. Identification, prioritization and quantitative characterization of near-field and far-field emission sources, adsorptive sinks, and air/surface chemistry and multimedia interactions would have a major positive impact on our ability to reduce uncertainty in the analysis of human exposure and subsequent risk. This basic research should be included in the current strategic plan because it is a large generic task that is not being done anywhere else in the world in a broad-based or comprehensive program.

Another element in figure 1-3 of the HHRS document that does not receive adequate attention in the document includes relating environmental concentrations to exposure concentrations and characterizing "contact" and intake/uptake mechanisms that describe the movement of chemical compounds onto and into the body.

Further, neither existing fate and exposure models nor data provide the temporal and spatial resolution necessary to support significant advances in research related to aggregate/cumulative exposures or research identifying highly exposed subpopulations. Increasing the resolution and the reliability of models and the relevance of data that represent the pre-exposure links will be particularly important to the successful of the proposed strategy.

The panel acknowledges that many of these pre-exposure research areas are covered in specific problem driven research (2-11, line 21; 7-3, line 21. problem driven research However, the document needs to provide information about these specific program areas and how that research will integrate with the exposure-to-effect research highlighted in the strategy.

Continued hypothesis-driven research to develop and evaluate these pre-exposure modeling and measurement techniques should be highlighted as an early and relatively high priority research area. Indeed, the entire HHRS Strategic plan should be examined to provide an appropriate balance of allocated resources such that the uncertainties associated with these early determinants of risk are reduced at the same rate as those related with the later biological events that culminate in adverse health effects. The panel recommends that the HHRS be revised to reflect on-going research, and current work plans on source-to-human exposure characterization and modeling. Hyperlinks to these relevant, specific exposure measurement, characterization, and modeling research programs should be added to the next iteration of HHRS.

The HHRS document emphasizes the importance of the combined and iterative use of measurements and models. Figures 1-5 and 1-6 show a process by which premises lead to measurements, measurements lead to models, models lead to better premises, and better premises lead to additional experiments and better-informed measurements In contrast r, the HHRS document also states that the ultimate objective is to develop an "integrated modeling framework" (page 2-12, line 14) or a "framework to link models all the way from source to human health effects" (page 3-10, line 3). This implies that the Agency expects to complete the iterative process of experimentation and discovery and arrive at a final, comprehensive modeling framework. It is not entirely clear that such a framework would have the desired effect of providing "more confidence in exposure-dose-response relationships" (page 3-10 line 4). Confidence in a model comes not from how many links or processes are included but rather from

how well the modeling framework as a whole has been validated. It is important to remember that there are theoretical, philosophical and practical issues that make validation of these complex modeling frameworks extremely difficult, if not impossible.

Although the ORD recognizes the importance of model evaluation, the HHRS document is unclear as to the general approach that will be taken to insure the accuracy of models or modeling frameworks before they are used in human health risk assessment or in the reconstruction of exposure from biomarker data or in the evaluation of public health outcomes. The dilemma is that collecting relevant data for evaluating the accuracy of a model is expensive and time consuming. Even if model predictions match measurements for a given scenerio, this only provides a snapshot comparison and does not assure that the model will perform adequately in a prospective or retrospective analysis or for a different scenario. The panel recommends that the HHRS document discuss how the Agency will evaluate the models and methods that are part of the strategy and insure their applicability and credibility.

The discussion of the exposure research related to identifying highly exposed subpopulations begins with the statement that the overall objective should be the development of a model (2-20, line 12) while in reality, the overall objective is to identify highly exposed subpopulations of children and important sources and pathways of exposure. Granted the steps required to develop a model are similar to those required to identify the highly exposed subpopulation. Nevertheless, the panel recommends that the overall focus be clarified in the document and placed on the outcome (i.e., identification of highly exposed individuals) rather than development of the model.

Although the panel agrees that a focus on aggregate exposures and cumulative risk is a major step forward in how the Agency establishes criteria for the protection of public health, the Agency should be cautious in the assumption of the “one paradigm fits all” approach to risk assessment. This approach may not be warranted, especially if resources are limited. For example, while it is true that intakes tend to result from multipathway/multiroute processes, it is not unusual from one pathway/one route combination to explain the preponderance of the exposure and the dose. In such cases, it may not be cost effective, or even desirable, to exhaustively investigate aggregate exposure and aggregate risk. It may be useful to identify early on which exposure and pollutants fall in this category so resources are allocated more effectively. It is important to recognize that uncertainties will never be completely eliminated. Even though the ORD recognizes the need for selection criteria to identify the most appropriate model (2-3, line 13) in the context of harmonizing risk assessment, similar criteria for model selection should also be part of the other model intensive areas of research in the strategy. This is particularly important as the number and complexity of models, continues to increase. The panel recommends that research to help identify the appropriate level of model complexity for a given exposure/risk scenario should be a component of the research on aggregate and cumulative risk.

Using pharmacokinetic models of the exposure-to-dose continuum in reverse for relating measured biomarker data to exposure is ambitious but clearly offers potential for reducing uncertainty in the risk assessment process. It should be noted however, that the statement: "Combined with proper modeling techniques and some knowledge of possible exposure patterns and measurement, biomarker data can be used to estimate dose and exposure"

is still a hypothesis. It remains unclear how or to what degree the variability and uncertainty related to physiological parameters in the population and/or to the specific exposure scenario will influence the ability to perform back calculations in the absence of additional measurements. However, even if these model lack the ability to characterize prior exposures based in biomarker data, well formulated models that have been evaluated for accuracy (validated) and advanced statistical methods should help to identify critical data needs and lead to measurement strategies that will improve our ability to perform these inverse calculations.

A possibility that needs to be recognized and incorporated into this research aggregate and cumulative risk is an awareness of potentially positive or adaptive biological responses associated with low-level exposures. It is anticipated that a U-shaped dose-response curve at low (environmentally relevant) concentrations of single and multiple compounds could be quite common. This information could be exceedingly valuable in identifying "practical thresholds" of human response in defined populations which in-turn could speak to the potential impact of any risk management activity aimed at lowering human exposure. The panel suggests that non-monotonic dose-response proximate to actual exposure levels is a potential outcome (hypothesis) that should be incorporated into this research.

A commendable feature of the proposed approach (and one of the underlying principles of the HHRS) is that the integrated strategy provides for the intimate collaboration among ORD's Laboratories and Centers, so that research findings and study results can be incorporated across research programs through feedback. This collaboration has existed in the past but in a less than transparent and consistent manner. In particular, the barriers to communication between the exposure and human health research programs at ORD need to be further eliminated for the HHRS to be successful. The HHRS document should explicitly address how findings from exposure research will be incorporated as one of the fundamental inputs to health research. The integration of this process with EPA's extramural research through NCER's STAR program is also a positive aspect of the strategy, although the mechanism for establishing a link is not yet specified in the HHRS document. It is also not clear, what role the Program and Regional Offices have now or will play in the development of the Strategy beyond issues such as the pesticides program. As the eventual users of the products from the research efforts, their ongoing participation is essential for the success of the HHRS. Our explicit recommendation is that communications and interactions between the various groups be proactively nurtured and supported within the plan.

Although the research areas described in the strategy are ambitious and will certainly require a longer commitment than a 5-10 year timeframe, there is opportunity for early interaction between modelers and experimentalists that can lead to rapid advances in the exposure and risk sciences. Specifically, improved communication among modelers, experimentalists (data collection) and public health experts across ORD and the external scientific community can open up a number of new opportunities for evaluating existing data and models and for identifying critical data and modeling needs.

V. SUSCEPTIBLE POPULATIONS

The reviewers commend the EPA for emphasizing susceptible populations as a high priority area in need of additional knowledge and research. Overall, the HHRS document is an excellent draft, and the panel strongly agrees with the overall goals of the section on Susceptible Populations. The panel acknowledges the multidisciplinary requirements of such research. The panel commends the Agency on its efforts to further develop the necessary scientific linkages between different parts of the Agency, between the Agency and other governmental agencies and university research centers, and the support of multidisciplinary research centers in and outside the academic community as described in the HHRS document.

Susceptible Populations in EPA's Human Health Research Strategy

The HHRS document describes research approaches to the question of susceptible populations in broad terms. Its focus is directed towards early development, but the potential impact of chemical exposures during advanced age is also acknowledged, as is the possibility of long latency, delayed effects. The reviewers would equally emphasize the need to conduct research on differently aged individuals, including children (page 21, "Effects Research"). The contributions of genetic predispositions and concurrent disease are also recognized. In strict biological terms, the scope of the research effort is reasonable; although the more detailed plans to follow is where the most intense examinations will be directed. Due to the deliberate brevity of the HHRS document, much of the research detail is not provided and leads to some degree of uncertainty about the research plan.

One major constituent of susceptibility closely tied to public health outcomes seems to be lacking in the research plan, however. The panel appreciates the legislative and regulatory boundaries placed on EPA, but questions whether the full public health implications of either effects or exposure data can be understood without evaluating them in a broader environmental context. Certain groups, often those that experience the highest levels of exposure, are vulnerable in many other ways as well. Such disadvantaged populations experience inequalities in health and social status that parallel what the planning document terms pre-existing disease. Such inequities comprise a collection of risks that logically fall within the arena of cumulative risks and that substantially alter an individual's response to environmental chemicals and the interaction between health status (such as disease states) and the environment. Some of these factors are listed on page 2-17, but primarily within the framework of exposure, although the executive summary mentions "stressors other than pollutants." Empirically, moreover, studies based on the developmental neurotoxicity of lead and PCBs demonstrate differences in susceptibility associated with the social environment, a phenomenon that has been termed effect modification. Experimental models can be devised to explore analogous variables in animal studies, and the ORD laboratories should be capable of undertaking such research. For example, in rats, the effects of "enriched" environments (large social groups, play objects) can be compared to those in rats raised in "deprived" environments (single housing, no play objectsThe panel recommends that ORD also utilize animals whose DNA repair genes or tumor suppressor genes are altered or deleted and/or whose proto-oncogenes are mutated or transposed and placed

under the control of strong promoters in order to model the cancer risk of similarly susceptible human groups.

The impact of factors such as neuropsychological states, threatening environments, exposure to environmental tobacco smoke, socioeconomic status, drug and alcohol abuse, and maternal and child nutrition on environmental health were not explicitly noted in the HHRS document. These factors interact with environmental chemicals and should be a leading focus of future research. The influence of these factors on genetics, age, and disease-specific susceptibility to the adverse effects of environmental chemicals must also be studied.

No direct mention is made of studies on how early exposure to contaminants may alter the development of organ systems and functions. The panel recognizes ORD's efforts in this area, but it is important for the HHRS document to indicate how such interactions may modulate the response to exposures later in life. For example, how do early exposures affect the development of the immune system, which, in turn could determine the outcome of cancer and non-cancer endpoints?

The research plan tends to emphasize the development and application of animal models (e.g., page 2-19, line 5, and on page 2-21, line 26). Animal models may be necessary to understand mechanisms of toxicity, but the extrapolation of risk estimates from animal data to risk assessment in humans, although frequently necessary in the absence of human data, is fraught with hazards and caries an inherent degree of lack of specificity and accuracy. In developmental toxicology, extrapolation from animal studies to predict the effects of chemicals on the developing human, although often yielding crucial insights, has also at times proven to be a misleading predictor of toxicity, sometimes underestimating, sometimes overestimating threats to human health. It is also important to realize that, for many human outcomes or diseases (e.g., arsenic and skin cancer), relevant animal models have yet to be developed. Animal research and human research need to be closely coordinated, and the validity of the animal models as representative of the human condition must be carefully determined and cautiously applied. Many animal studies, for example, including those conducted by EPA, have relied on single high-level exposures. These issues with animal models underscore the need for expanded human research, employing both controlled exposure and field studies. In summary, the panel supports the Agency's plans to develop and apply new animal models and also encourages Agency plans to conduct studies of certain kinds in humans, such as the acquisition of physiologically based pharmacokinetic and pharmacodynamic (PKPD) data, that do not endanger ethical guidelines.

The impact of stages of life, disease states, and genes on exposure and all aspects of PKPD should be addressed in full by the Agency. Each subsection (genetic, stage of life, and disease state) should be implemented within a full PKPD framework. The capacity of stage of life cycle to influence all the aspects of PKPD is well documented, although major gaps in knowledge still exist. The same in-depth discussion and approach is relevant for genetic issues and disease state-related effects. Against a background of impaired health, risk evaluations need to weigh how exposure to environmental chemicals toxins might further modify PKPD. The discussion on page 2-18, lines 25-28, should therefore be expanded to include all the PKPD parameters.

For example, the PKPD approach would practically or theoretically examine the effects of disease state. Certain disease states could alter both exposure and PKPD. One example may be children with autism or developmental delay who mouth their hands and toys to a greater degree than the average child. The adult with anemia may also have increased pica. The child experiencing an asthmatic attack may breathe more frequently and thereby be exposed to more air pollutants. Further, the adult or child with dermatitis may absorb chemicals transcutaneously more than the individual with intact skin. Certain illnesses that alter physiologic states prevailing during pregnancy can alter hepatic and renal clearance and also metabolic profile. In addition, host defense may be altered in humans who have cancer with a depressed host defense mechanism or who are receiving chemotherapy to treat cancer. The inclusion of the concept of how disease states alter PKPD parameters and consequently alter risk could be included in the section on page 20. The same approach can be taken with genetics, since genotype can alter exposure (genetic predisposition to autism), transport proteins, clearance, metabolic profiles, and end organ sensitivity.

End organ vulnerability is most often thought of when discussing disease states. The discussion here (page 2-18, line 4) examines how end organ effects may differ during various stages of development. For clarity, the HHRS document should state that specific adverse effects, ranging from functional impairment to anatomical birth defects, depend upon a restricted window of susceptibility during development. That is, the defect is secondary to an exposure at a specific stage of development.

The HHRS document should provide more specificity in defining, understanding, and identifying sensitive individuals in the human population subject to diseases that can be altered or induced by environmental exposures. These diseases include neurobehavioral function, asthma, and cancer. For example, for cancer, will the most susceptible populations be fetuses with germline mutations, such as Li Fraumeni Syndrome (germline p53 mutations), or Xeroderma Pigmentosum (XP), or Ataxia Telangectasia (AT), which, additionally, may come from economically disadvantaged, nutritionally disadvantaged, and perhaps also environmentally disadvantaged backgrounds? Or, will they constitute young children who have Li Fraumeni Syndrome, XP, or AT, are infected with Human Immunodeficiency Virus (HIV), have contracted Acquired Immunodeficiency Syndrome (AIDS), and are also economically disadvantaged? Recognition should be given to how the effect of polymorphisms in enzymes such as glutathione transferase and other enzymes would interact with these germline mutations in defining the most sensitive receptors. Defining and identifying these highly susceptible groups (”sensitive receptors”) is crucial in determining how the distributions of risks for these sensitive receptors will be modeled. The HHRS document should define the proposed susceptible subpopulations for many disease states, including cancer, in risk assessment. In the case of cancer, these could include those possessing various polymorphisms at various DNA repair loci, including but not limited to, XP and AT, and in drug metabolizing enzymes (glutathione transferase, cytochrome P450 enzymes, etc).

More specific details should be given in the section entitled, “Research on Susceptible and Highly-Exposed Subpopulations” (page 2-17). The HHRS document should define the proposed susceptible subpopulations for cancer risk assessment, including those

possessing various polymorphisms at various DNA repair loci (XP, AT) and in various drug-metabolizing enzymes (glutathione transferase, various cytochrome P450 enzymes, etc.).

No definition of susceptibility to cancer would be complete without taking into account the fact that cancer incidence increases as the fourth or fifth power of age. Translating this finding into data based on the emerging science of molecular epidemiology provides an opportunity to determine whether specific chemical carcinogens that are environmental pollutants do indeed contribute to cancer induction in humans at specific organ sites. That is, molecular biomarkers of cancer development can be used to trace a population response even if the exposure occurred during childhood.

All of these considerations emphasize why the plan should define susceptible populations in more detail, including identifying the biological reasons for the increased susceptibility, for example, including those with genetic, disease-related, and age-specific predispositions, and those uniquely exposed to environmental/occupational carcinogens. More explicit definitions will assist in the pursuit of mechanistic research based on susceptibility. The HHRS document should also describe how animals whose DNA repair or tumor suppressor genes are mutated or deleted or whose proto-oncogenes are mutated or altered would be utilized to model the cancer risk of similarly susceptible human groups.

In its discussions of aggregate and cumulative risk, the HHRS document refers to the Food Quality Protection Act (FQPA) as a useful example because it specifies a common mode of action as a criterion for calculating cumulative risk. Although the HHRS document recognizes the possibility of different modes of action (page 2-15), cumulative risk can also depend on common endpoints. For example, studies of the developmental neurotoxicity due to exposure to PCBs, lead, and methyl mercury have all employed IQ measures as criteria, but it is far from evident that the same mechanisms are responsible for the parallel outcomes. Certain populations, too, are known to experience elevated exposures to combinations of these agents, suggesting that commonalities among endpoints should play a role in cumulative risk models equivalent to commonalities among mechanisms. Put another way, elevated exposure to one (or class of) toxic agent may render that population more susceptible to the adverse effects of another (or class of) toxic agent. The HHRS document refers to such a possibility (p. 2-15) only glancingly. Quantifying commonalities in this situation is a challenging problem that deserves more exposition.

A problem complicating risk assessment and adding to uncertainties is the question of dose-response relationships. In most of its discussions of dose-response modeling and formulation, the HHRS document seems to accept the conventional assumption of monotonic dose-response functions. Especially since endocrine disruption gained prominence as an environmental health question, this assumption seems increasingly questionable, even for agents such as lead. Non-monotonic dose-response functions for both carcinogens and non-carcinogens have been the subject of recent conferences and federal government review panels. The panel believes that HHRS planning should more directly pursue this question because of its implications for linking exposure and effects and because of the role the Strategy accords exposure-response modeling.

Although uncertainties lurk in every aspect of risk assessment, a major source of uncertainty arises from the huge diversity of environmental exposures. This may be the most challenging question confronting attempts to link exposures to public health. New risk assessment prototypes may have to be developed to provide a coherent strategy for formulating the appropriate research. The HHRS document should clarify what EPA research (ORD) has achieved so far in reducing uncertainty in risk assessment. The reasons for proceeding along a specified research path are not clearly explained and need to be supported in a historical context.

The definition of susceptibility in the HHRS document leads to a discussion of how to take account of biological variability in populations. One source of variability is mostly overlooked, however. The current HHRS document does not explicitly recognize the importance of studying both sexes to determine susceptibility. Does ORD have stated policies about this issue? Even recent publications from the NHEERL show reliance on only one sex in experimental studies in the areas of inhalation toxicology and neurotoxicology. Given the vast differences in disease prevalence and risk factors seen in human populations, and, now, the importance attached to endocrine disruptors, the panel believes that unequivocal recognition of such differences should be incorporated into HHRS planning.

The multidisciplinary requirements in study design dictate the need for multidisciplinary cooperative efforts, both within the EPA and between the EPA, other governmental agencies, and environmental centers in universities. The EPA could also consider partnering with the National Cancer Institute (NCI), CDC, ATSDR and the NIEHS, to incorporate them into this multidisciplinary research framework. They could also partner with the Environmental Protection Agencies of the various States, such as the Office of Environmental Health Hazard Assessment of the California EPA, and with investigators at research institutes and universities, and encourage them to participate in this overall strategy of multidisciplinary research. This would maximize the strength of this overall research effort led and coordinated by the EPA. The EPA should lead this effort, conduct much of the research, and also co-ordinate the efforts of extramural scientists and regulators, where common interests exist in regulation of specific toxins and carcinogens. This cooperation would maximize efficiency of utilization of resources, strengthen the overall research effort, and eliminate redundant efforts.

The current HHRS document seems to be lacking in the identification of which major problems of human health fall within the scope of the strategy as defined by their impact on susceptible populations. What are the potential connections? A matrix—a speculative one, of course—should be constructed showing how specific public health problems may be linked to environmental exposures. The matrix entries might consist of ratings of the estimated strength of the association in categories of low, medium, and high along with degrees of uncertainty labeled in the same way. It is difficult to discern how risk management decisions can be assigned priorities if all problems are accorded equal status.

The HHRS document selects out cancer and neurodegenerative disease as two categories of diseases that are of particular interest in children. Reproductive, neurodevelopmental, and endocrine disorders should not be accorded less emphasis. The questions invoking the greatest concern could be explicated more clearly in the kind of matrix noted above. Perhaps the statement on page 2-24, line 17, should be explained in greater detail.

The HHRS document states that there is a plan to conduct much of their research on childhood asthma through the National Children's Study. This pivotal and critical statement should be explained in much more detail. The reasons to focus on asthma should be explained, and the reasons to de-emphasize other disease states should be discussed, particularly disease states that could have greater longitudinal impact on the nation. The National Children's Study should greatly enhance our grasp of those factors influencing susceptibility. It will not be definitive, however, because susceptibility is a complex function of many variables that will require much additional research to elucidate.

The overall intent of the Strategy is to reduce risk to the public from exposure to carcinogens and toxicants. Therefore, the impact of diet and lifestyle in cancer risk should also be considered, since these factors can significantly modify cancer risk, and in some cases are the predominating factors. In the case of prostate cancer, for example, caloric intake and dietary fat apparently contribute significantly to risk, thereby defining another type of susceptible subpopulation. In addition, effort should be made to identify the most potent carcinogens that the public is likely to be most heavily exposed to. Then, the EPA should conduct risk assessment on these highly carcinogenic chemicals to which the public is heavily exposed first, to mitigate levels of these chemical agents. Commencing this effort with a model genotoxic carcinogen, such as aflatoxin B1, where there is a plethora of data on aflatoxin B1-DNA covalent adducts in animals and in humans and synergism between hepatitis B virus infection and aflatoxin B1 exposure in liver cancer induction, and with a model non-genotoxic carcinogen, such as TCDD, whose effects are mediated through binding of TCDD to the AHH receptor and resultant influences on gene expression, is recommended. Modern risk assessment procedures should be first modeled on these two compounds, or similar compounds, to determine how difficult and expensive it will be, and how much effort it will require to develop and employ advanced risk assessment procedures. For example, new conceptual models using mathematical functions to describe uncertainty distributions for risk of exposure to each set of chemical toxicants or carcinogens will need to be developed. Distributions of risk, including risk for sensitive receptors, should be incorporated in the risk assessment calculations where feasible. It is also necessary, as the HHRS document recognizes, to develop appropriate risk assessment procedures for important mixtures of highly carcinogenic chemicals to which humans are exposed, and to determine whether the resultant risks are additive, antagonistic, or synergistic to populations exposed to these mixtures.

VI. EVALUATION OF PUBLIC HEALTH OUTCOMES FROM RISK MANAGEMENT ACTIONS

To date, the Agency has mainly focused on products (e.g., publications in the scientific literature or implementation of certain controls) or very broad measurements (e.g. number of children living in non-attainment areas) as indicators of the impact of its programs on environmental health. These measurements are not appropriate indicators of effectiveness in attaining the ultimate mandate of EPA, i.e., to protect public health and the environment. Therefore, the strategy's intent to measure outcomes is a move in the right direction. However,

this is an extraordinarily difficult task, and one to which EPA needs to devote considerable thought and effort before moving ahead with the formulation of a research plan in this area.

The panel agrees that the phrase "Public Health Outcomes" as used in this Chapter needs to be explained in more detail. The public health perspective is largely absent: it is axiomatic of public health that detailed mechanisms need not be completely elucidated prior to preventive action being taken. Furthermore, what the public health outcomes are or how they will be selected is not clear from the material presented. While the HHRS document mentions '(public health) outcome oriented goals and measures of success,' it is unclear throughout most of the HHRS document whether these outcomes are mostly health-related or also include pollution prevention measures or remediation end points as public health outcomes. In addition, the HHRS document does not make clear whether the research strategy is intended to address disease alone as a measure of health status, or whether it includes broader concepts such as wellness or quality of life.

Concerning measures of success, the panel found the opening paragraph of the Section (page 3-1) misplaced (environmental compliance costs seemed to be the tail waging the dog of public health protection). Moreover, since there is no discussion in the HHRS document of health costs analysis (disability, health care utilization, cost of lost life) it seemed very odd to begin the entire discussion in terms of cost and leave it at that. The (unintended) implication is that epidemiologic data will lend themselves to cost effectiveness studies or, worse yet, to some kind of cost-benefit analysis. This section of the HHRS document should be deleted (section 3, page 1, lines 4 to beginning of line 10).

There were no specific concepts of "epidemiologic studies" presented . Moreover, use of the term "population exposure studies" as if this were *not* [italics added] epidemiology. Both TEAM and NHEXAS are the current "gold standard" for exposure assessment) further confused the presentation ; i.e. population exposure studies could not simply be a subset of a general epidemiologic approach. Thus, the section is addressing two of four suggested approaches in a rather non-descript fashion. The panel recommends that greater detail be provided to clarify what type of epidemiologic study is meant (such as cohort, case-control, time-series, molecular epidemiologic studies). Additionally, the HHRS document implies in some of the examples chosen that measuring toxin levels in human samples (biomonitoring such as blood lead monitoring) might serve as a cornerstone of public health outcome assessment. The panel believes that this is a very reasonable approach to explore. Any analysis of such population-based data, testing for time trends or correlates of either exposure (with the biological monitoring as the dependent variable) or, if possible, disease outcomes (biological or health outcome monitoring as the independent predictor) would be an epidemiologic undertaking. Note that it will be, however, much easier to conduct ~~a~~ standard before/after comparisons evaluating remediation success and body burden reduction than to show that such actions result in health outcomes. The exception may be immediate changes in short-term health outcomes (such as changes in asthma symptoms during the Olympic games in Atlanta when it became mandatory for public transit to replace the usual traffic).

The panel agreed that it is an oversight that an explicit discussion of the concept of "biologic monitoring" is missing from this HHRS document. A better explanation of how

priorities would be set for which indicators to collect data via biological monitoring is needed, even by broad classes. A suggested starting point could be a review of the Toxic Release Inventory (TRI) data for the 30 largest volume substances together with a listing of matching and reasonably sensitive biologic markers (such as for metals, organo-chlorines, cholinesterase inhibitors, PAHs). This is especially relevant in light of the CDC pilot data from NHANES III. The inclusion of an example in this regard would help to clarify what the approach (and breadth) of the proposal is. For example, the EPA has modified its arsenic standard in drinking water. P erhaps a figure in the text or an appendix could show the relationship between arsenic ingestion and health outcomes and the impact of differing standards. The risk management decisions to lower the level would/should result in fewer arsenic health outcomes (skin cancers and bladder cancers, for example). How might research be conducted to demonstrate this impact from a rule change? The example could be expanded to provide some of the necessary approaches for research, surveillance, and additional analysis.

A reduction in exposure is an outcome that can be measured with current methodologies given sufficient resources. With models that are available today (or combinations of models), it may be possible to apportion the fraction of the decrease in exposure due to regulatory intervention, and the portion of the reductions in exposure that occurred consequent to changes in technology or other determinants, which might have occurred without regulatory intervention. Such case studies could be developed with currently available methodologies for lead, for example, for which there is a wealth of information for establishing the chain of events describing the continuum from emissions to health effects. There are significant historical data demonstrating the parallel between the decrease in airborne lead concentrations and blood levels that can be associated with the removal of Pb from gasoline (although this particular regulation was not directed at protecting the public from the health effects of lead, but was adopted as part of the ozone control strategy when catalytic converters were mandated). An improvement in health or decrease in disease resulting from regulatory enforcement, however, would be much more difficult to establish because of the many uncertainties in risk assessment and the multiplicity of technological and societal factors that affect health and disease status and trends in the population. It is possible, for example, for the Agency to promote a rule that actually decreases the risk for developing a particular disease but, simultaneously, societal and economic factors increase the probability of developing the disease through other mechanisms with a much larger net effect. Frequently, those societal and other factors are not recognized early in the process. Thus the Agency could deem a particular regulatory effort ineffectual and reverse its course, when in reality the rule or regulation had the effect it was intended in terms of public health protection. Thus, in the case of Pb, a health outcome measure would have to demonstrate, for example, improvements in IQ paralleling decreases in blood lead. IQ, however, is affected by many other societal factors and, in spite of the wealth of data and studies on Pb health effects that are available, it would be much more difficult to apportion the regulatory and non-regulatory determinants of improvements in IQ than of reduction in blood Pb. The Agency needs to engage more fully in an exercise of defining the characteristics of "health outcome measures" amenable to the purpose of tracking the effectiveness of the Agency's regulations.

Furthermore, in terms of epidemiologic approaches, the emphasis on data set linkages would be far more relevant were it connected to a discussion of prototypical epidemiologic approaches and their applicability and feasibility in the context of the stated goals.

For example, if the EPA considered a "sentinel health event"[c] approach, how would the events be chosen for which surveillance tracking might be established? The TRI database cross-tabulated with target organ effects might be a reasonable starting point. A tabular presentation of disease outcomes with a reasonable environmental population attributable risk would also be highly informative. This would not have to be all-inclusive but rather a starting point for the public feedback alluded to in the Appendix. Examples might include: Parkinsonism (manganese, carbon disulfide); aplastic anemia (benzene); bladder cancer (arsenic); skin cancer (UV); heat stroke deaths (meteorological conditions); and non-malignant respiratory mortality (particulate pollution). By definition, some of these disease outcomes would be studied through mortality records; others could be studied through a variety of other secondary data sources. The panel also suggested that while the HHRS document mentions some endpoints, a full range of "outcomes" should be considered, including biomarkers of exposure (vs. environmental measures), biomarkers of early effect (e.g., liver, kidney function changes), child development, toxic endpoints, disease endpoints, behavior changes, and social-community changes~~, etc., etc~~. It seems fairly clear that unlike the biologic monitoring component, these studies would not be based on an EPA lead in primary data collection. Thus a primary/secondary data dichotomy might be useful to define.

Within the secondary data analysis realm, it is likely that certain epidemiologic techniques will be more important than others, but this discussion is also lacking in the draft document. There is not even a reference to time-series analyses, for example. Also it is not clear that compiling existing databases will be helpful since most of these databases were constructed to comply with regulatory standards or serve other needs than to supply adequate data (at the individual level) for meaningful epidemiologic studies that could lend themselves to drawing causal inferences. It would be much more helpful to evaluate each of these databases with respect to usefulness for epidemiologic exposure or outcome assessment at the individual or ecologic level. For example, if these data can only be used at an ecologic level, one will have to address problems, in epidemiologic terms, concerning the "ecologic fallacy ". The issue of tracking manifestations of disease in non-humans as a marker of human health outcomes should also be considered; this would provide a linkage between epizoonotics and human epidemiologic studies (e.g. West-Nile virus).

Furthermore, if the ultimate goal is to establish linkages between sources, environmental concentrations, exposure, effects, and effectiveness of management actions, and - assuming that effects refer to health effects - this most likely means that individual level human data has to be collected. It is not clear how this can be accomplished in an adequate manner without designing specific and appropriate epidemiologic studies for each question under consideration. It was noted that all examples for effectiveness evaluations for diverse risk management actions cited are examples from non-environmental areas (vaccination etc) in which it is possible to collect individual level exposure and outcome data. These examples are inappropriate as models for assessing the effectiveness of reducing environmental pollutants at the population level especially if widespread low-level contamination in large populations is a concern and for which there most likely will be no easy means of linking exposures to individual

[c] Sentinel health events methodology refers to the identification of target conditions for surveillance in research based on the likelihood that individual cases may be attributable to the specific risk factors of interest.

health outcomes. Questions such as whether an action prevented, reduced, eliminated, or modified a disease outcome may not only be difficult, but impossible to answer for most chronic and complex diseases with multiple risk factors and etiologies. The research goals should be calibrated with these major limitations in mind.

Finally, a discussion of the challenges associated with risk reduction evaluation of complex diseases is missing from the draft document. Fundamental to this is recognition that the fact that most diseases have multiple risk factors and pathways or so-called competing risks. A comparison of estimates derived from risk assessment models to actual health outcome rates predicted by the model may depend on the prevalence and importance of other causal or modifying or competing factors for a complex disease. Therefore, the reduction of just one (environmental) risk factor may or may not lead to a reduction of the prevalence/incidence of a health outcome that depends upon a multitude of factors. These factors may be increasing or decreasing concomitantly (e.g. a reduction in air pollution and an increase in asthma rates in the former East-Germany does not lend itself to the conclusion that air pollution causes or exacerbates asthma). Taking the example of lead exposure reduction and cognitive impairment, not only would it be methodologically difficult to show longitudinally that a reduction of blood lead levels in children leads to improved cognition, this direct linkage may not be necessary. Biological monitoring data demonstrating a decreased lead burden would be scientifically sufficient to support a positive health impact in light of established dose-response relationships and consistent with accepted principles of public health that emphasize prudent intervention in the absence of incomplete certainty. Furthermore, a systematic (generic) framework for all before/after comparisons is problem-ridden since each complex disease will have its own unique challenges and most likely will require a custom tailored epidemiologic approach. In order to establish any trends in disease over time, it may be necessary ~~to~~ not only to measure the disease in question (such as asthma) consistently but we may also have to wait generations or decades to see these trends - periods too long for any policy making purposes.

VII. CONCLUSION

The Human Health Research Strategy (May 2002 --Draft- HHRS) outlines the ORD's vision for core research in human health risk assessment over a 5 to 10 year horizon. The HHRS document represents a remarkable effort to outline a strategic research direction for what is arguably the premiere research organization on this subject in the world. The HHRS document is comprehensive and well written. The HHRS is well thought-out relative to the various elements that need to be considered, with an emphasis on long-term core research to reduce uncertainty in human health risk assessment using a multidisciplinary research approach the intramural research capabilities of the individual ORD Laboratories and Centers, and extramural research sponsored by ORD. The conceptual framework and general directions outlined in the HHRS provide direction and focus for the ORD's Multiyear Plan on Human Health Research. The Multiyear Plan, in turn, influences the development of individual program work plans on the project level at ORD Laboratories and Centers. These individual project level work plans will likely influence research outside of the Agency through a range of funding mechanisms. Thus, the strategic research directions described in this document can, and likely will have a direct impact on the overall focus of the community of risk assessment research, both

within and outside the ORD. The authors are to be congratulated for the hard work and hard-won insights evidenced throughout this HHRS document. Indeed, it provides an invaluable service to the broader scientific community just in the deliberation and presentation of the various definitions. Upon even modest reflection, it is clear that the identification, construction, and implementation of a plan that will guide the ORD's core human health research program over the next decade will be an exceedingly difficult but important task. Most important is that the very recognition of this need is quite significant and worthy of commendation from the risk assessment community.

A substantive concern is the breadth of the proposed strategy in the context of a 5 to 10 year plan, and given the state of the science of the various disciplines that will address the areas of uncertainty described in HHRS document (summarized in pages E-3 to E-4). The overall plan is highly ambitious, even if collaboration and partnering with other agencies is a guiding principle, and considering that the research objectives are directed at the fundamental principles and factors that underlined the effects and the exposures leading to those effects. There is a broad range of scientific uncertainties that may not be addressable in the proposed time frame. For example, the nature of pollutant mixes is so complex that we are more likely to have a longer list of research questions than any firm answers within the proposed time frame. Judicious selection of "case studies" is a reasonable approach.

The two – prong research strategy directed at 1) addressing and reducing significant uncertainties in human health risk assessment, and 2) developing and introducing measures that track the public health effectiveness of regulatory mandates of the Agency are clearly delineated in the HHRS document. The first strategic direction is consistent with the ORD's and Agency's strategic goals, and it is clearly responsive to many comments and suggestions from the SAB and external scientific review panels of the Agency's programs. The second prong of the strategy moves beyond the typical "product" measures of effectiveness to the ultimate question of the impact of the Agency's action on public health.

ORD's plan to focus on developing a multidisciplinary, integrated program that will build linkages between exposure, dose, effect and risk assessment methods to provide the scientific basis for harmonizing risk assessment approaches, predicting aggregate and cumulative risk, and protecting susceptible subpopulations is highlighted in great detail. In addition, the effort that ORD will apply to develop an integrated research program utilizing its intramural scientific capacity in conjunction with extramural grants, cooperative agreements, and interagency agreements is clearly described. The importance of the efforts that have been and will continue to be made to identify and foster collaboration with other Federal and State agencies, as well as academic and private organizations having research programs that complement ORD's research efforts is well articulated. The panel encourages these efforts and believes that they are essential for the ultimate success of the overall strategy.

VII. APPENDIX

Other Comments

The HHRS document is well written with few typos. On page viii of the glossary, in the third line of the Childhood definition, it should read "…starting with pre-conceptive exposures of the parents…" instead of "…to parents". Also, the age definition of childhood is vague and it should be made consistent with that of other Agencies, such as the CDC.

The definition of "core" and "problem driven" research needs to be clarified because EPA's definition and use of these qualifiers is different from the general understanding of the public and other sectors of the scientific community. Figure 1-1 should be reconsidered since it does not provide a clear understanding of core or problem drive research. Perhaps it could be replaced with a list of examples.

The discussion and strategy related to molds needs to be revised (pages 1-10/11). Some of the statements on the relevance of S. chartarum to asthma causation/exacerbation are incorrect. It is also disconcerting for the Agency to focus on an exposure variable that is not an entity amenable to regulatory action, and should be considered instead as a co-factor in the investigation of the effects from agents that fall within the preview of the Agency.

Page 3-1 (second para): "EPA risk assessors and risk managers must consider the uncertainties associated with the risk assessment process" does this also include the upper as well as the lower bounds of such uncertainty i.e. a possible range of effects or could this be used to discredit efforts related to risk assessment? Note that there will be many instances in which it is impossible to reduce uncertainties without postponing decisions indefinitely. Also what criteria will be used to decide whether uncertainties are too great to proceed…? Finally, it may not be possible to reduce uncertainty factors, in certain cases additional information may indicate a larger multiplier and thus uncertainty. The point is that uncertainty factors should be data driven and to the extent possible moiety specific.

In regard to Section 3.1, 1 the invocation of efficacy v. efficiency is in any way relevant to the model of environmental interventions, as useful as they may be for a vaccine trail. I would recommend deleting this and the related box. Definitions that might be relevant include biological monitoring, primary v. secondary prevention, sentinel health events, and population attributable risk.

Page 3-2 (first para): The sentence on lines 1-7 of 3-2 is constructed in a way suggesting the ban on leaded gasoline reduced cognitive development. Also note that while studies examining the effect of lead on cognition showed a negative impact of blood lead levels on cognition there was, however, no study done to assess the impact of lead reduction on cognition. Rather studies conducted after the lead ban used reductions of blood lead levels as biomarkers of exposure and

had those serve as proxy for 'increased levels on cognition' but not studies of improvement of cognition (which would be hard to impossible to conduct).

Page 3-2 (last para): please note that while the tracking of priority chronic diseases may have rightfully been recommended by PEW 2000 this is a future goal and currently not supported by law or financial means (especially not at the National level)
The boxed statement on page 3-2 is not illuminating.

Following the discussion of the NRC 1997 on 3.2, I was expecting some mention of Health People 2010 and its follow-up. Isn't there some mention of diseases and public health goals relevant to ambient environmental factors?

The last paragraph of the opening section on page 3-3 could easily be deleted.

Page 3-4 (first para): 'understanding the efficacy of an EPA decision requires a comparative analysis of risks before and after implementation of risk management action"; again it is not clear whether 'after' refers to health outcome research or pollution reduction and modeling of prevented fractions etc. If health effects are meant it would be important to define what 'after' represents, i.e. in the case of chronic disease such as cancer this could mean waiting decades. Much of section 3.2 on page 3-5 reads as a second introduction, with another whole series of caveats. What is the point of this section and how does it differ from the opening introduction?

Page 3-5 (first para): health risks do not only dependent on multiple sources for a pollutant (i.e. sources which may or may not be controlled by a management decision) but also on multiple necessary component causes that add up to a sufficient cause for the health outcome under consideration.

Page 3-5 (first para): in the last sentence, behavior of individuals cannot only reduce risk but also exposure (use of bottled instead of tap water).

Page 3-5 (second para): This paragraph states that the "optimal approach is to compare a health risk assessment before and after the risk management action has been employed". This sentence is confounded, i.e. why should one perform the risk assessment twice, i.e. isn't the risk assessment predicting the risk under several exposure scenarios so one just needs to compares the higher versus lower exposure risk estimates? What may be implied here is that the estimate from the risk assessment should be compared to the actual health outcome rates predicted by the model?

Page 3-5 could include some discussion on research limitations in addition to uncertainties. These would include disease latency, individual variability, degree of compliance (to strategy or behavior), size of the population, population mobility (in-outmigration), exposure misclassification, causality of relationships/associations, and other confounding factors.
Page 3-8(second para): case studies are suggested for licensing new substances into the environment. Please note that such study will per se not allow human health risk assessment and we need to rely on animal data.

Page 3-9: (middle para): this whole paragraph's meaning is completely obscure.
Page 3-9, lines 23-31. This gets into the PEW Commissions' and agencies (eg. CDC and ATSDR) health tracking research and surveillance activities. Text is not clear how EPA and others will work together on this.

Page 3-9: (last para): "as a first step … use existing approaches" not clear whether any exist, which ones are meant apart from the inappropriate ones (vaccination trials) cited above.
Page 3-10: (first para): This goal seems very elusive and extremely hard to achieve especially in real world scenarios of ubiquitous and low level exposures, multiple concurrent exposures and different susceptible populations.

Page 3-10: (second para): does involving stakeholders at all levels imply that the best model will be selected by vote or consensus rather than according to science?

Page 3-11: (third para): "develop a comprehensive state-of- the art science evaluation in consultation with….. decision makers.." not clear what decision makers have to do with state-of the art science evaluations; shouldn't scientists do this?

Page 3-11, next steps. Not clear on what intramural and extramural research approaches may be taken to address the next steps. Could use stronger words like "research partnerships" so that we all are connected in what we do and learn, and apply what we find out. The Next steps section is also a place to "identify the risk management actions (ultimately policies and regulations on a broader scale) that could be the target for evaluation research." Can this strategy approach better address the previous GAO critique of human exposure assessment and lack of coordination and research among federal agencies? We have an opportunity to show marked progress within this proposed strategy.

In Section 3.3, the effectiveness/efficacy distinction is not helpful. In terms of the box, it suggests that there is no intermediate or short-term goal only a long term one. Is that true?
The earlier comments on lack of specificity are most relevant to sections 3.4 and 3.5. It must be noted that these sections, that should be the heart of the matter, are only slightly over 4 pages, with 7 pages of material that is fundamentally introductory.

Very few of the Figures arc helpful to the reader and some, such as 1-2, verge on the silly.
The word "sensitive" as in sensitive populations should be used with caution lest it unintentionally imply immune sensitivity. Is susceptible part of what is intended?

Specific reference to other living systems early on in the HHRS document would be useful.

Although citing an example such as molds may be useful, the figure in question should be asthma specific and the text, in focusing on stachbocttys and alluding to pulmonary hemosiderosis, is counter-productive.

The term "in silico" is quite unfortunate.

Figure 3-1. There are additional concepts for understanding the role of analysis of health outcomes and areas for research needed for the arrows presented in the diagram.

Section 3.1. Evaluating public health outcomes from risk management decisions could take on many different types of approaches. The paper suggests correlational approaches that are fairly indirect, but require a good understanding of linkages between exposure and health outcomes. Other approaches could include comparative studies of different risk management actions for similar communities (same contaminants, pathways, etc.). For example, action 1 vs. action 2….then the best one vs. action 3, etc…. building an effective strategy toward the most effective approach. Quasi-controlled studies will help in comparing options/actions across communities. Before and after approaches are OK, but also have limitations with lack of control for other factors that may be temporal in nature.

Section 3.1. ATSDR conducted a study of a community with high soil concentrations of lead. The cleanup involved a "checkerboard" approach in remediation of yards for homes with small children. Over the years we were able to show that the children in homes with remediated yards had lower blood lead levels than non-remediated homes with small children. This is but one example of an innovative strategy to prove effectiveness of risk management decisions.

Arrow from research to evaluation of health outcomes: this would include causal criteria for considering the outcomes to study/monitor, including strength of association, consistency of association, temporality of association, specificity of association and biological plausibility. The linkage should be established so that there is better estimation and support for any estimated/measured health improvements.
Arrow from risk assessment to evaluation of health outcomes (add one): this would include the validation of models.
Arrow from risk management to evaluation of health outcomes: there is a need for research and understanding of the efficacy, effectiveness, responsiveness, and degree of compliance in the risk management action.

Editorial Comments on Section 3:

Page 3-2, line 3 should read …..”tracking of **reduced** blood-lead levels in children as a result of the ban, and **epidemiological** studies confirming the linkage between elevated blood levels and reduced cognitive development in children.”

Page 3-5, line 6. should read…..”health risks are **influenced by** other sources **and factors** not **under** consideration.”

Page 3-5, line 8. should read…..”Behaviors of individuals **and communities** in reducing risk are **additional** important variables.

Page 3-5, line13. should be ….”scientifically, **the predictability of risk** management action effectiveness **would be** more accurate.”

Page 3-5, line 18-19. amend to …" systematic **evaluation** framework for doing so does not exist. Prospective assessments of risk often use **multiple** approaches with varying degrees of sensitivity, **uncertainty**, and reliability."

Page 3-5, line 22. add…."statistical power to detect the expected risk reductions **in the size of community impacted**."

Page 3-6, text box, long-term goal. Actually it is the effectiveness of public health **interventions** resulting from risk management actions (not the outcomes per say; the outcomes can be a measure of success or failure) This text is somewhat confusing and is imbedded several places in the HHRS document.

Page 3-6. The questions listed (lines 8-13) do not track with the KEY questions in the text box. The first question should add "..policies, regulations, **or actions**" and this should be changed throughout the HHRS document.

Page 3-6, line 20, add…."on the contributions **and collaboration with** a number of.."

Page 3-7, line 1 add…."**In close collaboration with other research partners,** ORD's…"

Page 3-7, lines 11-20. I'd suggest that these two objectives standout with a header or be included in the text box on page 3-6.

Page 3-7, line 18 add…"by which **EPA and** others can measure or **predict** changes…"

Page 3-8. first paragraph. The use of the words "cases" or "case study" are not appropriate. An alternate word would minimize any confusion that epidemiologists might have here and elsewhere in the HHRS document.

Page 3-8, line 8. Add …."will be placed on policies, regulations, **or actions** attendant…"

Page 3-8, lines 27-30. These are the most important and KEY questions to be addressed by researchers. Also, remember the WHO definition of health would include mental well-being and quality of life, not just the absence of disease. There may be social-behavioral impacts that could be evaluated.

Page 3-9, line 1. Modify to keep parallel thoughts on what is being done as opposed to just saying epidemiologic studies….."(a) **health outcome/impact studies** related to environmental exposures, (b)…"

Page 3-10, lines 21-26. The development phase should include working with partners and stakeholders to determine what is available and needed.

Page 3-10, lines 28-31. The investigation phase needs to be done in close collaboration with partners and stakeholders in developing a multi-year research plan based on the identified needs.

Page 3-11, lines 4-7. The delivery phase will overlap with the investigation phase, since some discoveries and findings will result early on as opposed to other risk management actions, rules or regulations. It is not clear who the audience of the "compendium" is and who would need training and be targeted.

Page 3-11. The next steps might be presented in a model/diagram that shows the continuous cycle of review, intervention, evaluation, review…

Appendix D, page A-5. *For some unknown reason, ATSDR is not mentioned in this section. I could develop text that EPA can use. We conduct lots of applied research addressing community and tribal health issues and environmental exposures. We also maintain and develop many health and exposure registries and surveillance systems.*

Appendix E, page A-8. Under Health Effects Databases, I'd suggest adding the National Health Interview Survey (NHIS) for NCHS and the Social and Behavioral Risk Factor Survey (SBRFS) for CDC. Also, CDC does have access to databases maintained by states for cancer, birth defects, birth outcomes, deaths, etc. I'd add state agencies as responsible for hospital discharge and emergency department electronic databases.

Appendix E, page A-8. Under Health and Environmental Databases, I'd suggest adding Poison Control Centers (ATSDR and CDC are working together to get electronic datasets including acute and chronic poisonings). Under ATSDR, I'd add "registries" that follow-up individual health outcomes on communities and populations exposed to specific environmental contaminants (benzene, TCE, TCA, dioxin, tremolite asbestos). Under ATSDR, I'd also add HSEES (Hazardous Substances Emergency Event Surveillance system) that collects information about environmental releases, the event, victims, response, and outcomes (for acute events including industry fires, spills, transportation accidents, etc.) from a range of state databases. The system is currently active in 16 states with about 6,000 events per year.

Another issue is the "retrospective" nature of the proposed research effort. Understandably, studies can be undertaken in an attempt to estimate the health impact of past risk management actions that perhaps could provide insights and help to develop new approaches, as the Strategy indicates. However, the most effective way of incorporating an impact evaluation tool is at the time of deciding what the action should be, that is, the outcome measure should be used prospectively as an integral part of the risk management process. It is not clear that the current Strategy envisions research on a framework for defining outcome measures that could be integrated within the risk management decision process.